Antipsychotics and Diabetes

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Objectives

- Describe the cardiovascular risk of mental health disorders and diabetes
- Describe the metabolic side effects of atypical antipsychotic medications
- Review the ADA/APA/AACE/NAASO Consensus on Antipsychotic Drugs and Obesity and Diabetes

Antipsychotic Agents

First Generation Chlorpromazine (Thorazine) Perphenazine (Trilafon) Trifluoperazine (Stelazine) Thiothixene (Navane) Haloperidol (Haldol) Fluphenazine (Prolixin)	Extrapyramidal side effects Tardive Dyskinesia
Second Generation (AKA - Atypicals) Clozapine (Clozaril) - 1989 Risperidone (Risperdal) - 1993 Olanzapine (Zyprexa) - 1996 Quetiapine (Seroquel) - 1997 Ziprasidone (Geodon) - 2001 Aripiprazole (Abilify) - 2002	Metabolic side effects Advantages: Tx Negative symptoms Improves mood Prevents relapse

Schizophrenia and Diabetes

- Limited epidemiological data
  - increased prevalence of obesity, impaired glucose tolerance, and type 2 diabetes in people with psychiatric illness
- Schizophrenics, independent of treatment
  - two-fold increased risk of diabetes mellitus compared to the general population.

Schizophrenia and CVD

- More than **two thirds** die of CVD
  - Compared with 50% in the general population
- More prevalent cause of death than suicide

Hennekens CH et al. Schizophrenia and increased risks of cardiovascular disease. Am Heart J. 2005 Dec;150(6):1115-21.

Schizophrenia and Metabolic Syndrome

- Higher prevalence
  - abdominal obesity
  - elevated TGs
  - high blood pressure
- 2 to 3 times more likely to meet metabolic syndrome criteria than general population

Diabetes and Antipsychotics

- Drug surveillance and retrospective analyses
  - association between specific SGAs and both diabetes and obesity
- UK Case-control study
  - SGA and FGA to be 4.7 and 1.7 times greater to develop diabetes compared to non-users respectively

Kornegay CJ, Vasilakis-Scarmozza C, Jick H, et al. Incident Diabetes Associated with Antipsychotic Use in the United Kingdom General Practice Research Database. J Clin Psychiatry 2002;63:758-62.

SGAs: Diabetes

- More frequent with the SGAs than the FGAs
  - risk greatest for clozapine and olanzapine
- Hyperglycemia can be seen within a few weeks of initiating drug treatment
- Hyperglycemia may resolve after the medication is discontinued
- Recurrent hyperglycemia after re-challenge

SGAs: Weight Gain

- Rapid increase in body weight in the first few months of therapy
- May not reach a plateau even after 1 year
- Limited data suggest that most of the weight gained is fat
  - canine model indicates increase total visceral fat mass and intrahepatic lipid content

SGAs: Dyslipidemia

- Changes in serum lipids correlate with changes in body weight
- Clozapine and olanzapine
  - greatest weight gain
  - greatest increases in TC, LDL, and TGs and with decreased HDL cholesterol

2004: Second Generation Antipsychotics (SGAs)

- FDA mandates changes in labeling
  - Warnings for hyperglycemia and diabetes
  - Affects all atypical antipsychotics
- Consensus Development Conference on Antipsychotic Drugs & Obesity & Diabetes
  - Aripiprazole and ziprasidone
    - Little/no weight gain
    - Little/no diabetes
    - Little/no dyslipidemia

Diabetes Care 2004; 27:596-601.

ADA/APA/AACE/NAASO Consensus on Antipsychotic Drugs and Obesity and Diabetes: Monitoring Protocol

	Base	4 wks	8 wks	12 wk	Qtrly	12 mos.	5 yrs.
Personal/family Hx	X					X	
Weight (BMI)	X	X	X	X	X		
Waist circumference	X					X	
Blood pressure	X			X		X	
Fasting glucose	X			X		X	
Fasting lipid profile	X			X		X →	X

**More frequent assessments may be warranted based on clinical status*

***Diabetes Care.* 27:596-601, 2004**

Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)

- Multi-center, NIMH-sponsored
  - 18 months
- “Real World” setting
  - Concomitant medications, medical illnesses, substance use disorders allowed
- Effectiveness (Phase 1)
  - Published in NEJM 2005

Medications in CATIE

- First Generation
  - Fluphenazine (Prolixin)
- Second Generation (AKA - Atypicals)
  - Clozapine (Clozaril)
  - Risperidone (Risperdal)
  - Olanzapine (Zyprexa)
  - Quetiapine (Seroquel)
  - Ziprasidone (Geodon)

CATIE Summary

- 74% discontinuation rate for all drugs
  - Consistent with practice and clinical trials
- Weight and metabolic side effects
  - Clozapine and olanzapine > quetiapine and risperidone
- Ziprasidone
  - least weight and metabolic effects

CATIE Summary

- Perphenazine
  - less costly than other medications
  - not significantly or substantially less effective
- SGAs may be most effective in the refractory schizophrenia

Summary

- Consideration of metabolic risks when starting SGAs
- Patient, family, and care giver education
- Baseline screening
- Regular monitoring
- Referral to specialized services, when appropriate

Questions?